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RESPONSE TO IMMUNOTHERAPY IN A 20-MONTH-OLD BOY WITH ANTI-NMDA RECEPTOR ENCEPHALITIS



Encephalitis associated with antibodies against the NMDA receptor (anti-NMDA-R) is characterized by prominent psychiatric symptoms, dyskinesias, seizures, autonomic instability, and central hypoventilation.¹ We report a 20-month-old boy with oral-buccal dyskinesia, choreoathetosis, seizures, and encephalopathy, consistent with anti-NMDA-R encephalitis.

Level of evidence. This report is Class IV evidence and is a single observational study without controls.

Case report. A 20-month-old boy had a pruritic maculopapular rash over his face, trunk, and arms for 2 weeks without preceding fever or illness. A week later, he developed involuntary tongue thrusting and right hand twitching. He spoke less and became less interactive. On admission, his temperature was 39.2°C. Examination showed oral-buccal dyskinesia and choreoathetosis, particularly the upper extremities (video on the *Neurology*[®] Web site at www.neurology.org). Complete blood count showed a white cell count of $15.6 \times 10^9/L$ with neutrophilic predominance. CSF revealed slightly elevated total nucleated cells of $5/\mu L$ with lymphocytic predominance (65%), normal protein (24 mg/dL), glucose (59 mg/dL), and lactate (1 mmol/L) concentrations. Nasogastric tube was placed owing to impaired oropharyngeal coordination. Prolonged video EEG recorded several generalized seizures from sleep. There was no electrographic correlate with the involuntary movements, which persisted during wakefulness and sleep. Brain MRI and magnetic resonance spectroscopy on day 2 were normal.

Bacterial cultures in the blood, urine, and CSF were negative. Serologies and PCRs in the serum and CSF were negative for infectious etiology (table e-1). Investigations for inborn errors of metabolism and toxins were unrevealing. Antistreptolysin O, anti-DNAse, peripheral blood smear, vitamin E, copper, ceruloplasmin, homovanillic acid, vanillylmandelic acid, thyroid peroxidase antibody, and CSF neuro-

transmitters were unremarkable. Antineuronal nuclear antibody-1, -2, -3, anti-glial/neuronal nuclear antibody-1, Purkinje cell cytoplasmic antibody-1, -2, antibodies to acetylcholine receptor (AChR) binding, ganglionic AChR, striated muscle, amphiphysin, collapsin response-mediator protein-5, N-type calcium channel, P/Q-type calcium channel, and voltage-gated potassium channel were negative. Repeated CSF, EEG, MRI brain, and CT of the chest, abdomen, and pelvis were normal. A conventional cerebral angiogram was negative for small vessel vasculitis.

Trials of clonazepam, amantadine, haloperidol, carbamazepine, levetiracetam, and valproic acid had minimal effect on his movement disorder. Seven infusions of IV immunoglobulin (IVIg) 2 g/kg/day twice weekly and prednisone 2 mg/kg daily were started on day 30 for presumed postinfectious encephalitis. A percutaneous gastrostomy tube was placed on day 47 because of 10% weight loss. Because improvement had been minimal, prednisone was replaced by a 5-day pulse methylprednisolone 10 mg/kg daily on day 58.

Antibodies to the NMDA-receptor were subsequently identified in the CSF obtained prior to initiation of IVIg. Rituximab was started on day 66. At dismissal on day 71, the patient required G-tube feeding and wheelchair due to the movement disorder. Medications at dismissal included valproic acid for seizures and dyskinesia, weekly rituximab 375 mg/m² for a total of 4 infusions, and IVIg 0.4 mg/kg once every other week.

One month after dismissal, the oral-buccal dyskinesia and choreoathetosis significantly reduced. All immunotherapy was discontinued. Three months later, the patient had no involuntary movement, took food by mouth only, and ambulated independently. One year after diagnosis, he continued speech therapy for apraxia. Follow-up CSF anti-NMDA-R was not performed due to clinical improvement.

Discussion. A distinct movement disorder in women with ovarian teratoma and anti-NMDA-R encephalitis comprises semi-rhythmic bulbar and limb movements that persist during prolonged periods of unresponsiveness.² Our 20-month-old patient

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showed oral-buccal dyskinesia and choreoathetosis, which continued during sleep. In retrospect, the distinct movement disorder which persisted during sleep should have been an early diagnostic clue. About 40% of adult patients and 73% of pediatric patients with anti-NMDA-R encephalitis have no identifiable tumor.^{1,3} The majority of patients with anti-NMDA-R encephalitis have a prodromal viral-like syndrome, even those with tumor.¹ Extensive analysis of CSF, brain biopsy, and autopsies in other patients has failed to implicate viral pathogenesis.¹ IVIg and corticosteroids have been tried with variable efficacy in patients with anti-NMDA-R encephalitis without tumor.^{4,5} For those patients who do not respond to IVIg and corticosteroids, rituximab, an anti-CD20 monoclonal antibody, may expedite recovery.⁶ Rituximab has been safely used in children with opsoclonus-myoclonus syndrome, which may have similar lack of response to IVIg and steroid.⁷ Although clinical improvement correlated temporally with rituximab in our patient, a delayed effect of IVIg and steroid therapy, or spontaneous recovery of the disease, cannot be excluded. To our knowledge, this is the youngest patient with anti-NMDA-R encephalitis described to date. The case highlights the importance of considering this autoimmune entity in children with unexplained encephalopathies associated with movement disorders. Early immunomodulatory therapy with agents including rituximab should be considered in such cases, as it may hasten recovery.

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Disclosure: Dr. Wong-Kiesel and Dr. Ji report no disclosures. Dr. Renaud serves on the editorial board of Pediatric Neurology. Dr. Kotagal serves on the editorial board of Pediatric Neurology and has received research support from Boehringer Ingelheim. Dr. Patterson has served on scientific advisory boards for Actelion Pharmaceuticals Ltd., Shire plc, and StemCells, Inc.; has received fund-

ing for travel from Actelion Pharmaceuticals; serves as Editor for Up-To-Date and Pediatric Neurology; and receives research support from Actelion Pharmaceuticals Ltd. and from the NIH (1U54NS065768-01 [Co-I]). Dr. Dalmau has received honoraria for lectures not funded by industry; receives research support from EUROIMMUN and the NIH/NCI [RO1CA107192 (PI) and RO1CA89054-06A2 (PI)]; has received license fee payments from EUROIMMUN for an NMDA receptor autoantibody test (patent pending PCT/US07/18092, filed: August 15, 2007); and has received royalty payments and may accrue revenue for US Patent 6,387,639, issued May 14, 2002: Patent for Ma2 autoantibody test. Dr. Mack serves as the Book Review Editor of Neurology® and on the editorial boards of Pediatric Neurology, the Journal of Child Neurology, and Brain and Development.

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